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General approach to dry cough

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ABSTRACT

Dry cough is a common health problem and upper airway cough syndrome, asthma and gastroesophageal reflux disease are the most common causes of dry cough in adults. Diagnostic approach and algorithms are defined according to the American Academy of Chest Diseases cough guideline updated in 2006. The initial evaluation should start with history taking, physical examination, radiologic and spirometric assessment. Antihistaminic and decongestant agent combinations, inhaled corticosteroid and bronchodilator combinations, leukotriene receptor antagonists, and when necessary oral steroids are used in the treatment depending on the etiology. Treatments based on etiology and if needed evaluation with further tests are essential.

Keywords: Dry cough, etiology, diagnosis, treatment

INTRODUCTION

Although cough is a natural defense mechanism that protects the respiratory tract, it is also a symptom of all respiratory system diseases and some non-respiratory system pathologies.[1-3] Its incidence in the adult age group is between 3-12%. A simple and anatomical cough algorithm was first introduced by Richard Irwin in 1977.[4] The American College of Chest Physicians (ACCP) modified these guidelines in 2006.[1] This protocol defines the cause of cough based on the structures within the anatomical distribution of the vagal afferent nerves.[5,6] Coughing is a forced expiratory maneuver against the glottis which is closed after a deep and rapid inspiration. Meanwhile, the contraction of the expiratory muscles of the chest and abdomen generates a high intrathoracic pressure, the sudden opening of the glottis forcefully expel air from the mouth, and while passing through the vocal cords air produce coughing sound. Afferent stimuli created via receptors in the diaphragm, pleura, bronchi, trachea, larynx, pharynx, nasopharynx, nasal mucosa and external auditory canal travel through N. vagus, N. trigeminalis, N. Phrenicus, N. glossopharyngeus to the voluntary cough center in the cortex and the reflex cough center in the brain stem. Efferent stimulus formed by the N. vagus, N. phrenicus and spinal motor nerves creates cough response via contraction of the diaphragm and other respiratory muscles.[7]

A dry cough is defined as a cough that does not bring up any phlegm or mucus. Dry cough is often due to an underlying disease or a defense mechanism of the respiratory system against irritation, and it can last from a few days to a few weeks. It is classified according to the duration of the cough; acute cough <3 weeks (most common), subacute cough 3-8 weeks, chronic cough >8 weeks.[7]

Symptoms commonly associated with dry cough are tickling sensation in the airways, wheezing, dyspnea, pressure sensation in the chest, inability to sleep especially at night due to coughing, deterioration of sleep quality and a cough that sounds unproductive.[8] Other findings accompanying dry cough include flu-like symptoms (fatigue, fever, sore throat, headache, etc.), runny or stuffy nose, sore throat, vomiting, swollen neck lymph nodes, joint pain, loss of appetite, and diarrhea.[9]

Table 1 . Causes of dry cough

- Cough associated with upper respiratory tract
- Gastroesophageal reflux (GER)
- Cough variant asthma (CVA)
- Cough due to angiotensin converting enzyme inhibitors (ACEIs)
- Nonasthmatic eosinophilic bronchitis (NAEB)
- Chronic idiopathic cough (cough hypersensitivity syndrome)
- Cough due to obstructive sleep apnea syndrome (OSAS)
- Exposure to acute irritants
- Occupational asthma
- Chronic psychogenic cough
- Chronic lung diseases

COUGH ASSOCIATED WITH UPPER RESPIRATORY TRACT

Cough due to upper respiratory tract pathologies should also be considered Dry cough that develops due to upper respiratory tract related pathologies is called "upper airway cough syndrome". Upper airway cough syndrome is associated with many upper respiratory tract pathologies with allergic, infectious, vasomotor etiology and irritating particles. The most common cause of cough is respiratory tract infections caused by viruses. In recent years, the relationship between chronic

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tonsillar enlargement, external auditory canal pathologies, obstructive sleep apnea syndrome (OSAS) and cough has also been described.[10,11]

in patients with normal chest X-ray, non-smoker, using agents other than angiotensin converting enzyme inhibitor (ACEI) and with symptoms such as throat clearing due to nasal discharge.[12]

However, postnasal discharge is not the only pathophysiological mechanism in dry cough seen after upper respiratory tract infection and it may not always be detected on physical examination. In their study Macedo et al.[13] reported that postnasal discharge may not be the only cause of dry cough Cough receptors located in the upper airways have been shown to be more sensitive in cough associated with the upper airways.[14] Diagnosis is made by symptoms, physical examination, radiological findings, and response to specific treatment. Empirical use of antihistamines alone or in combination with decongestants due to their anticholinergic effects is the first treatment choice.[1,2-15]

Sinus radiography should be performed in cases that do not respond to empirical treatment. Bacterial sinusitis, perennial nonallergic rhinitis and allergic rhinitis may be the underlying cause1.[12]

Cough associated with an upper airway infection usually resolves within three weeks. Although to a small extent, Bordetella pertussis might be cause persistent cough. If secretion has subsequently started in the upper airways, the diagnosis is mainly based on culture and Polymerase Chain Reaction (PCR) in the samples taken from upper ways. Azithromycin is used for treatment.[16]

GASTROESOPHAGEAL REFLUX (GER)

Normally, GER is functionally occurring 10-15 times a day during meals, after meals, and during the REM sleep phase. Microaspirations can cause coughing by producing irritation in the hypopharynx and supraglottic larynx or by stimulating the esophago-bronchial reflex at the lower esophageal level and creating chronic inflammation.[17] Three mechanisms have been identified in the onset of GER; persistent low sphincter pressure, temporary relaxation of the esophageal sphincter, and increased intra-abdominal pressure.

In addition to dry cough, if chest X-ray is normal, GER should be considered in the first-place patients with gastrointestinal system (GIS) complaints and heartburn.[17]

GERD can be diagnosed using empirical treatment without any medical examination. Antacid therapy should be applied to patients with a typical history, even if they do not describe any GI symptoms. Endoscopy, barium esophageal radiography, esophageal impedance measurement, esophageal manometry, ambulatory intraesophageal pH monitoring can be performed to confirm the diagnosis. The most sensitive and specific test for GERD diagnosis is 24-hour esophageal pH monitoring, however, usually anamnesis would be enough. For patients who do not show any improvement with treatment 24-hour esophageal pH monitoring is indicated. Treating reflux with acid-blocking drugs (proton pump inhibitors), sleeping on a high pillow, diet and lifestyle changes may help to ease the symptoms.[1,2] If the symptoms persist despite full compliance with antireflux treatment and lifestyle changes, and for those whose cough does not regress after three months of treatment, antireflux surgery can be considered. [3]

Laryngopharyngeal reflux is the retrograde flow of a small amount of gastric content into the larynx and intermittently during the day. Unlike GER, it does not cause symptoms in the esophagus, gastrointestinal and respiratory systems. Dry cough is detected in 97% of those with laryngopharyngeal reflux and the diagnosis of laryngopharyngeal reflux is performed using video-laryngoscope.[18]

COUGH VARIANT ASTHMA (CVA)

Cough may be the only symptom in 7-11% of asthma patients, and they might not have a history of wheezing, dyspnea, or asthma; this condition is called cough variant asthma. Salem and Aviado, in 1964, reported for the first time a cough due to airway obstruction and stimulated cough receptors by local bronchoconstriction.[19] Cough can occur without bronchospasm, in fact, cough can be the only symptom in 28% of asthmatic patients.[20] In patients with suspected asthma based on anamnesis, the diagnosis is confirmed by pulmonary function tests, reversibility test, daily PEF measurement, or bronchial provocation test if necessary. If bronchial provocation test cannot be performed, CVA can be diagnosed based on the response to treatment and empirical treatment should be initiated. Even if a treatment response is achieved, one should keep in mind that chronic cough causes such as nonasthmatic eosinophilic bronchitis and irritant exposure cannot be ruled out. Inhaled corticosteroids and bronchodilators are recommended for the chronic cough seen in CVA and complete recovery may require 6-8 weeks of treatment. If there is airway inflammation and increased eosinophil count, anti-inflammatory therapy can be started for the cough resistant to inhaled corticosteroids and in case of more resistant cough short-term (1-2 weeks) systemic corticosteroid can be given.

COUGH DUE TO ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIS)

Cough due to ACEIS first described in 1985, the underlaying mechanism is not fully known.[21] It has been reported that mediators such as bradykinin and substance p activate ACEIs. Treatment may be insufficient when dry cough occurs due to increased estrogen levels in pregnant women, decreased immunity and the inability to use most of the drugs. Cough emerges in 5-35% of patients treated with ACEIs.[20] This side effect is more common in non-smokers, women, black people, and Asians.[22] The best treatment option is discontinuation of the drug unless it is not contraindicated. Patients can switch to another treatment group and if the cough resolves ACEIs can be restarted.[2-23] Although, the cough disappears 1-4 weeks after the discontinuation of the drug, this process can take up to three months. Sodium cromoglycate, theophylline, indomethacin, amilodipine, nifedipine, ferrous sulfate can be used to suppress cough in patients for whom ACEIs cannot be discontinued.

Cough due to COVID-19 is like the symptoms of upper respiratory tract cough syndrome. Its treatment is the same as for upper respiratory tract cough syndrome.[24]

NONASTHMATIC EOSINOPHILIC BRONCHITIS (NAEB)

Non-asthmatic eosinophilic bronchitis (NAEB) is an important cause of chronic cough and characterized by eosinophilic infiltration of the airways.[25] Although it is known that occupational exposure and allergen exposure play a role in the etiology of the disease, it is not fully understood yet. Methacholine response and variable airway obstruction are not present in these patients.

It was first described as one of the causes of chronic cough in 1989 by Gibson et al.[7] Cough may be dry or not, the absence of bronchial obstruction should be demonstrated by pulmonary function tests, reversibility test, if necessary bronchial provocation test. Diagnosis is based on demonstration of >3% eosinophilia in sputum, induced sputum, and sometimes bronchial lavage or bronchoscopic biopsy in patients who did not smoke, has no symptoms and functional impairment due to airway obstruction and airway hypersensitivity. These tests may not be performed in cases with a dry cough. The best treatment strategy is to avoid exposure. Initial treatment is low-dose inhaled corticosteroids, in advanced cases, high-dose inhaled corticosteroids or oral corticosteroids should be considered. Cessation of smoking is important for symptom relief. However, the differential diagnosis of NAEB and cough variant asthma (CVA) may be difficult in patients who have treated response.[26]

CHRONIC IDIOPATHIC COUGH (COUGH HYPERSENSITIVITY SYNDROME)

The diagnosis of idiopathic cough is based on exclusion of others. The diagnosis of idiopathic cough should not be made before all diagnostic procedures are completed, specific and empirical treatments have been tried, and rare causes have been excluded. It is also known as sensory neuropathic cough, laryngeal sensory neuropathy, sensory hyperreactivity, and cough associated with vagal neuropathy.[6] Hyperalgesia is present in idiopathic coughs as in other neuropathic diseases. The concentration of neuropeptides is increased at the nerve endings that act as cough receptors in the airways. Magnetic resonance imaging (MRI) shows increased activation in cortical and subcortical centers associated with cough.[27] In a study in experimental animals, qualitative changes with increased expression of tachykinin in airway sensory neurons and nonnociceptive neurons were observed in animals inoculated with Sendai virus. This type of phenotype changes may cause increased cough reflex sensitivity and cough even after viral upper respiratory tract infection.[28] Another study in patients with idiopathic cough reported an increase in lymphocytes in the bronchial epithelium and bronchoalveolar lavage fluid (BAL).[1] The effect of sex hormones was emphasized as the reason why idiopathic cough is common in women. Generally, upper respiratory tract infections is common in menopausal women. Usually, there is a feeling of irritation and itching in the throat before coughing starts. Bad smells, food, talking, exercise, cold weather are the most common triggers. Non-respiratory complaints such as urinary incontinence, chest and back pain, deterioration in social relations, anxiety and depression are also prominent.[6] In a study by Ebihara et al.[29] danazol helped regression of cough in female animals with ACEI-induced cough.

COUGH DUE TO OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

OSAS should also be considered in unexplained coughs. The treatment response rate is 93% to Continuous Positive Airway Pressure (CPAP) treatment together with other treatment combinations.[11]

EXPOSURE TO ACUTE IRRITANTS

Irritants with high solubility, such as ammonia, cause mild symptoms in the upper airways, as patients will be irritated due to their foul smell. On the other hand, irritants with low solubility, such as ozone, are inhaled for a longer period of time, and they can cause serious airway damage and dry cough or irritant cough. Immunological, irritant, corrosive agents in the workplace can also cause dry cough .[7]

OCCUPATIONAL ASTHMA

Occupational asthma is a type of asthma caused by exposure to inhaled irritants in the workplace. Asthma symptoms such as dyspnea, cough, wheezing, and tickling usually regress or even improve after being away from the workplace. Usually, dry cough is the main symptom in occupational asthma patients.[30]

CHRONIC PSYCHOGENIC COUGH

It is common in childhood, and it may be habitual or part of a tic disorder. It may occur spontaneously or voluntarily. Cough usually disappears during an enjoyable activity or night and day sleep. A diagnosis of psychogenic cough should not be made without excluding all other causes.[7]

CHRONIC LUNG DISEASES

Dry cough can be seen in chronic bronchitis, tuberculosis, bronchiolitis, interstitial lung diseases, and lung cancer. Other rare causes are heart failure, external auditory canal diseases, diaphragm irritation, peritoneal dialysis, laryngeal sensory neuropathy, arteriovenous malformations, retrotracheal masses, premature ventricular beats.

STUDIES FOR INVESTIGATING THE ETIOLOGY OF DRY COUGH

Chest and sinus radiographs, pulmonary function tests (reversibility and bronchoprovocation tests with methacholine), allergy tests, tests for gastroesophageal reflux, microbiological or cytological sputum examinations.[17]

TREATMENT OF DRY COUGH

Treatment Strategies in Dry Cough

If possible, the first step is cessation of smoking.[1-3] Studies have shown that active or passive smoking increases incidence of dry cough.[31] Occupation and hobby inquiries should be made.[1,2,3] Symptoms and signs of specific diseases should be evaluated in patient history and physical examination and a Chest X-ray should be performed. In cases where treatment was started and cough persists despite this treatment, stopping the treatment and monitoring the cough response may give clues for the etiology.[2] Generally, the chance of treatment of the

cough is better when the cause of the cough is determined, and specific treatment is given. This is the basis of the cause-based treatment model.[1,2,32]

Sometimes it is an option to wait for the dry cough to resolve on its own in 1-2 days. Criteria for applying to a physician in dry cough are fever, hemoptysis, dyspnea, severe chest pain, wheezing, being in the same environment with a patient with COVID, whooping cough or tuberculosis, facial swelling or rash, confusion, sleep problems, neck lymphadenopathy.

Ambulatory treatment of dry cough may include taking plenty of fluids, honey, salt mouthwash, clearing the throat with water when the cough urges, not using the voice excessively, avoiding triggers such as extreme cold and dry air, using an air humidifier, cold steam, or an air cleaner.

Treatment of dry cough has two types: Specific and nonspecific.

Nonspecific Treatment

It is the symptom remover treatment. It is not oriented to the cause or mechanism of coughing. It is preferred for cases when cause could not be detected or specific treatment could not be conducted. Irwin is applied so as to keep couging under control and relax patient. Since it depends on no reason, success ratio of nonspecific treatment is limited. Primary medicine used in nonspesific treatment is codein, dextromethorphan, dextropheniramine and pseudoephedrine.

Specific Treatment

It is oriented to the cause coughing. Success ratio is 84-98%.

In asthma-related dry cough, a combination of inhaled corticosteroid and long-acting b2 agonist is given. The cough seen in coughing asthma and eosinophilic bronchitis also has a high response to inhaled steroids. Cough resolves within 1 week after starting inhaler therapy. The definite benefit will be in 4-8 weeks. Leukotriene receptor antagonists alone or in combination with antihistamines are another option used in asthma patients with asthma and cough.[33-34]

Intranasal corticosteroid new generation antihistamine decongestant or decongestant alone are useful in allergic rhinitis, which is one of the subgroups of postnasal drip syndrome treatment. In vasomotor rhinitis, the anticholinergic agent ipratropium bromide responds better. In sinusitis, the appropriate combination of antibiotics, antihistamines and decongestants is used.[33-35]

Treatment of GER consists of lifestyle changes, drug therapy and surgical treatment. Quitting smoking in coughs occurring in GER, keeping the head elevated while lying down, losing weight, diet rich in protein and low in fat, avoiding foods and beverages (alcohol, coffee, cola, onion, chocolate) that cause relaxation of the lower esophageal sphincter have been beneficial in most people.[34]

Proton pump inhibitors are the most effective drugs used in coughs in GER. High doses (eg lansoprazole 30-60 mg/day) are used for 3 months. Other drugs used; prokinetic agents (cisapride, metoclopramide, etc.), H2 receptor blockers (famotidine, ranitidine, etc.).[33-34]

In the treatment of ACE inhibitor-induced cough, discontinuation of the ACE inhibitor is the most successful treatment. The cough resolves approximately 3-4 weeks after the drug is discontinued.[33]

Postinfectious cough goes away on its own. In cases that do not pass, short-term oral or inhaled steroids or ipratropium bromide are used. Macrolides are effective in pertussis. The common cold responds well to first-generation antihistamine-decongestant therapy.[35]

When other causes of dry cough (eg bronchial carcinoma, bronchiectasis, sarcoidosis, etc.) are treated, the cough improves.[35]

Inhaled anesthetic agents, gabapentin and codeine administration are recommended for the symptomatic treatment of cough in end-stage patients with malignancy and in all treatment-resistant cases.[21] In general, common causes with simple treatment schemes should be given priority, etiologies requiring long term treatment should later be considered.[15]

Causes of Dry Cough Requiring Urgent Treatment

Dyspnea, saturation decrease, tachycardia, tachypnea, pain or painful cough while breathing, high fever, rib fracture, rectus abdominis rupture, pneumoperitenum, pneumomediastinum, frequent urination may require urgent treatment. Urgent treatment should be performed after the etiology has been determined.[15]

In patients whose cough cannot be controlled despite advanced treatment, such as idiopathic cough or cough hypersensitivity syndrome, chough should be treated as a disease rather than a symptom, and suppressive therapies may be considered. This kind of treatment includes peripherally acting suppressive drugs (moguistein, levodropropizin), centrally acting suppressive drugs (codeine, dextromethorphan), neuromuscular blocking drugs (succinylcholine), drugs acting on mucociliary factors (hypertonic saline, erdosteine, carbocysteine, acetylcysteine, glycerol, bromhexidine, guafenesin, ipratropium bromide) .[7]

Complications of dry cough may occur if left untreated or in persistent cases. These complications can be sorted according to the systems as follows .[7]

Table 2 . Complications of cough

Respiratory complications	Subcutaneous emphysema Asthma attack Intercostal hernia Pneumothorax Pulmonary interstitial emphysema Tracheobronchial trauma Pneumomediastinum Pneumoperiteneum Pneumoretroperitoneum *Pneumocystis intestinalis* Laryngeal trauma.
Musculoskeletal complications	Rib fracture Rupture of rectus abdominis
Cardiovascular complications	Arterial hypotension Unconsciousness Bradyarrhythmia, tachyarrhythmia Rupture of subconjunctival, nasal or anal veins Displacement of intravascular catheters
Neurological complications	Syncope Seizure Headache Cerebral air embolism Cerebrospinal fluid rhinorrhea Disruption of ventricular shunt Stroke due to vertebral artery dissection Acute cervical radiculopathy
Gastrointestinal complications	GER Inguinal hernia Spleen rupture Hydrothorax in peritoneal dialysis Gastrostomy problems
Genitourinary complications	Urinary incontinence Cystocele
Other complications	Impaired quality of life Sleep disturbance Fatigue Weakness Vomiting Voice change Petechiae and purpura

CONCLUSION

Dry cough is an important health problem, and it is essential to clarify the etiology. In cases where the cause of the cough is known exactly and specific treatment is given, the chance of controlling the cough is high. However, cough treatment is based on the cause and in the form of an empirical treatment approach in practice. In patients whose cough doesn't resolve despite empirical treatment, the causes of cough should be investigated, and the treatments should be regulated.

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REFERENCES

1. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 Suppl):1S-23S
2. Morice AH, McGarvey L, Pavord I; British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. *Thorax*. 2006;61(Suppl 1):i1-i24. doi:10.1136/thx.2006.065144
3. Pavord ID, Chung KF. Management of chronic cough. *Lancet*. 2008;371(9621):1375-1384. doi:10.1016/S0140-6736(08)60596-6
4. Irwin RS, Rosen MJ, Braman SS. Cough. A comprehensive review. *Arch Intern Med*. 1977;137(9):1186-1191. doi:10.1001/archinte.137.9.1186
5. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis*. 1981;123(4Pt1):413-417. doi: 10.1164/arrd.1981.123.4.413
6. Birring SS. Controversies in the evaluation and management of chronic cough. *Am J Respir Crit Care Med*. 2011;183(6):708-715. doi:10.1164/rccm.201007-1017CI
7. Mülazimoğlu D, Kayacan O. Approach to chronic cough. *Tuberc Thorax J*. 2017;65(3):227-236. doi: 10.5578/tt.57253
8. Goldsobel AB, Kelkar PS. The adult with chronic cough. *J Allergy Clin Immunol*. 2012;130(3):825-6. doi: 10.1016/j.jaci.2012.05.057
9. Erkekol FÖ. Management modalities of chronic cough in adults. *Turk Thorac J*. 2013;14(3 Suppl):27-34. doi: 10.5152/ttd.2013.107
10. Birring SS, Passant C, Patel RB, et al. Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough. *Eur Respir J*. 2004;23(2):199-201. doi: 10.1183/09031936.03.00066403
11. Sundar KM, Daly SE, Pearce MJ, Alward WT. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. *Cough*. 2010;6(1):2. doi: 10.1186/1745-9974-6-2
12. Irwin RS, Curley FJ, Grossman RF. Diagnosis and treatment of symptoms of the respiratory tract, Armonk, N.Y. Futura Publishing Company. 1997:1-54.
13. Macedo P, Saleh H, Torrego A, et al. Postnasal drip and chronic cough: An open interventional study. *Respir Med*. 2009;103(11):1700-1705. doi: 10.1016/j.rmed.2009.05.005
14. Tatar M, Plevkova J, Brozmanova M, Pecova R, Kollarik M. Mechanisms of the cough associated with rhinosinusitis. *Pulm Pharmacol Ther*. 2009;22(2):121-126. doi: 10.1016/j.pupt.2008.11.014
15. Chummun D, Lü H, Qiu Z. Empiric treatment of chronic cough in adults. *Allergy Asthma Proc*. 2011;32(3):193-197. doi: 10.2500/aap. 2011. 32.3432.
16. Kline LW, Smith EA, Tracy LR ,Moerschel SK. Pertussis: a remerging infection. *Am Fam Physic*. 2013;88(8):507-514.
17. Özdilekcan Ç. Chronic Cough in Adults: Etiologic, diagnostic and treatment related approaches. *Celal Bayar Univ J Sci*. 2018;5(2):47-51.
18. Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA*. 2005;294(12):1534-1540. doi: 10.1001/jama.294.12.1534
19. Salem H, Aviado DM. Antitussive drugs, with special reference to a new theory for the initation of the cough reflex and the influence or bronchodilators. *Am J Med Sci*. 1964;247:585-600.
20. Dicpinigaitis PV. Chronic cough due to asthma. *Chest*. 2006;129(1 Suppl):75-79. doi: 10.1378/chest.129.1_suppl.75S
21. Kohno S, Ishida T, Uchida Y. The Japanese Respiratory Society guidelines for the management of cough. *Respirology*. 2006;11:135-186. doi: 10.1111/j.1440-1843.2006.00920_1.x
22. Irwin RS. Unexplained cough in the adult. *Otolaryngol Clin North Am*. 2010;43(1):167-180. doi: 10.1016/j.otc.2009.11.009
23. Lacourcière Y, Brunner H, Irwin R. Effects of modulators of the renin-angiotensinaldosterone system on cough. *J Hypertens*. 1994;12(12):1387-1393.
24. Karaca B. Clinical manifestations of COVID-19 in the adult age group. *J Biotechnol Strategic Health Res*. 2020;1:85-90.
25. Lai K, Chen R, Lin J, et al. A prospective multicenter survey on causes of chronic cough in China. *Chest*. 2013;143(3):613-620. doi: 10.1378/chest.12-0441
26. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough:eosinofilic bronchitis without asthma. *Lancet*. 1989;333(8651):1346-1348.
27. Birring SS. The search for the hypersensitivity in chronic cough. *Eur Respir J*. 2017;49(2):1700082. doi: 10.1183/13993003.00082-2017
28. Carr MJ, Hunter DD, Jacoby DB, Undem BJ. Expression of tachykinins in nonnociceptive vagal afferent neurons during respiratory viral infection in guinea pigs. *Am J Respir Crit Care Med*. 2002;165(8):1071-1075.
29. Ebihara T, Sekizawa K, Ohrui T, Nakazawa H, Sasaki H. Angiotensin-converting enzyme inhibitor and danazol increase sensitivity of cough reflex in female guinea pigs. *Am J Respir Crit Care Med*. 1996;153(2):812-819. doi: 10.1164/ajrccm.153.2.8564137
30. Alberts W, Brooks S. Advances in occupational asthma. *Clin Chest Med*. 1992;13(2):281-302.
31. Janson C, Chinn S, Jarvis D, Burney P. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. *Eur Respir J*. 2001;18(4):647-654. doi: 10.1183/09031936.01.00098701
32. Irwin RS, Curley FJ, French CL. Chronic cough: The spectrum and frequency of causes, key components of diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis*. 1990;141(3):640-7. doi: 10.1164/ajrccm/141.3.640
33. Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defence mechanism and as a symptom. A consensus panel report of the American College of the Chest Physicians. *Chest*. 1998;114(2):133S-181S. doi: 10.1378/chest.114.2_supplement.133s
34. Morice AH, Committee Members (ERS Task Force). The diagnosis and management of chronic cough. *Eur Respir J*. 2004;24(3):481-492. doi: 10.1183/09031936.04.00027804
35. Irwin RS, Widdicome J. Cough. In: Murray JF, Nadel JA (eds); Textbook of Respiratory Medicine. WB Saunders Company, NewYork. 2000;553-566.